BIOGRAPHICAL SKETCH

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NAME: McGinnis, Christopher Swart

eRA COMMONS USER NAME (credential, e.g., agency login): cmcginnis92

POSITION TITLE: Postdoctoral Fellow

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Wesleyan University	BA	05/2014	Biology; Biochemistry; Science in Society
UC San Francisco	PhD	09/2021	Cell Biology, Genomics, Bioinformatics
Stanford University	Postdoctoral	Present	Immunology, Cancer Biology, Genomics,

A. Personal Statement

My research leverages single-cell analysis, high-throughput genomic and chemical compound screens, and traditional cancer immunology approaches to uncover mechanisms of pro-metastatic immune reprogramming. Beyond discovering basic principles of metastatic cancer immunology, I hope to improve human health by developing the first-generation of anti-metastatic immunotherapies. Noting these interests and goals, **I plan to pursue these directions as a full-time academic researcher.**

My interests are inspired by my doctoral and postdoctoral training in genomics, bioengineering, and cancer immunology. As an NCI F31 Fellow in Dr. Zev Gartner's lab at UCSF, I developed single-cell genomics methods such as DoubletFinder (**McGinnis**, et al., *Cell Systems*, 2019) and MULTI-seq (**McGinnis***, Patterson*, et al., *Nature Methods*, 2019) that are widely-used by the single-cell community. Moreover, I built my foundation in immunology (**McGinnis**, et al., *BMC Biology*, 2021), metastasis biology (Winkler, Tan, Diadhiou, **McGinnis**, et al., *JCI*, 2024), and high-throughput screening (Jiang*, Chen*, Tsou, **McGinnis**, et al., *BioRxiv*, 2023). After completing my PhD, I joined Dr. Ansu Satpathy's group at Stanford as a CRI Fellow and PICI Scholar. I have received world-class mentorship at Stanford and leveraged these resources to discover new immunological mechanisms driving breast cancer lung metastasis (**McGinnis**, et al., *Cancer Cell*, 2024). I have also developed an *ex vivo* tissue culture platform that is amenable for anti-metastatic immunotherapy drug screens.

1. **McGinnis CS**, Murrow LM, Gartner ZJ. "DoubletFinder: doublet detection in single-cell RNA sequencing data using artificial nearest neighbors." *Cell Systems*. 2019; 8(4):329-37.e4. PMCID: PMC6853612.
2. **McGinnis CS**,* Patterson DM*, et al. "MULTI-seq: sample multiplexing for single-cell RNA sequencing using lipid-tagged indices." *Nature Methods*. 2019; 16(7):619-26. PMCID: PMC6837808.
3. **McGinnis CS**, et al. "No detectable alloreactive transcriptional responses during donor-multiplexed single-cell RNA sequencing of peripheral blood mononuclear cells." *BMC Biology*. 2021; 19(1):10. PMCID: PMC7816397.
4. **McGinnis CS**, et al. "The temporal progression of lung immune remodeling during breast cancer metastasis." *Cancer Cell*. 2024; S1535-6108(24)00167-3. PMID: 38821060.

*denotes equal contribution

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2024-present Metastasis Research Society Early Career Leadership Council
2023-present Scholar, Parker Institute for Cancer Immunotherapy
2022-present Irvington Postdoctoral Fellow, Cancer Research Institute
2021-present Postdoctoral Fellow, Stanford University
2020-2021 F31 Predoctoral Fellow, National Cancer Institute
2019-2020 Scholar, ARCS Foundation
2017-2020 Biochemistry Instructor, Post-Baccalaureate Program, UCSF School of Medicine
2016-2021 Graduate Student, UCSF
2014-2016 Research Associate I, Institute for Systems Biology
2012-2014 Teaching Assistant, Wesleyan University
2013 Undergraduate Research Assistant, University of Connecticut School of Medicine
2011-2013 Undergraduate Research Assistant, Wesleyan University

Honors

2023 Parker Institute for Cancer Immunotherapy Scholar Award
2022 Cancer Research Institute Irvington Postdoctoral Fellowship Award
2021 Society for Laboratory Automation and Screening Innovation Award
2021 Harold M. Weintraub Graduate Student Award (nominated)
2020 National Cancer Institute Ruth L. Kirschstein National Research Service Award (F31)
2019 Keystone Symposium Future of Science Fellowship
2019 UCSF Program for Breakthrough Biomedical Research
2019 UCSF Catalyst Award
2019 Mary Anne Kota Kimble Seed Award for Innovation
2019 ARCS Foundation Scholar

C. Contributions to Science

C1. Characterization of tumor-immune interactions in cancer and metastasis

Tumors dynamically and systemically remodel the immune system to metastasize and avoid anti-tumor immune responses. During my graduate and postdoctoral work, I used single-cell genomics analysis to generate nuanced insights into the tumor-mediated changes in immune cell state, population structure, and intercellular signaling networks that occur in diverse and clinically-relevant contexts. For example, I performed both longitudinal (**McGinnis**, et al., *Cancer Cell*, 2024) and cross-sectional (Winkler, Tan, Diadhiou, **McGinnis**, et al., *JCI*, 2024) analyses of the lung immune microenvironment in myriad murine models of metastatic breast cancer, revealing new mechanisms of pro-metastatic immune remodeling. I have also extended these experimental and analytical approaches to understand the dynamic primary tumor immune compartment in the context of increased neoantigen load due to *Tyw2* deletion (Waller*, Bartok*, **McGinnis***, et al., 2024, in review), as well as the role of $EPOR^+$ dendritic cells in immunological tolerance (Zhang X, **McGinnis CS**, et al., 2024, in review). My specific role in the longitudinal lung immune analysis project involved conceiving the project, performing all experiments and bioinformatics analyses, and writing the manuscript. For the cross-sectional lung immune analysis (collaboration with Dr. Zena Werb's group at UCSF), *Tyw2* neoantigen load (collaboration with Dr. Yardena Samuels' group at the Weizmann Institute), and dendritic cell tolerance (collaboration with Dr. Edgar Engelman's group at Stanford), projects I generated scRNA-seq datasets, performed bioinformatic analysis, and/or contributed manuscript writing.

1. **McGinnis CS**, et al. "The temporal progression of lung immune remodeling during breast cancer metastasis." *Cancer Cell*. 2024; S1535-6108(24)00167-3. PMID: 38821060.
2. Winkler J, Tan W, Diadhiou CMM, **McGinnis CS**, et al. "Dissecting the contributions of tumor heterogeneity on metastasis at single-cell resolution." *Journal of Clinical Investigation*. 2024; in press.
3. Waller C*, Bartok O*, **McGinnis CS***, et al. "Translation dysregulation in cancer as a source for targetable antigens." 2024. In review.

4. Zhang X, **McGinnis CS**, et al. “Erythropoietin receptor on cDC1s dictates immune tolerance.” 2024. In review.

C2. Single-cell genomics computational method development

The single-cell genomics field took a dramatic step forward in 2015 with the advent of droplet microfluidics for high-throughput single-cell RNA-sequencing (scRNA-seq). This innovation increased the throughput of scRNA-seq by multiple orders of magnitude, enabling entirely new kinds of biological questions to be addressed at single-cell resolution. More recently, droplet microfluidics applications have also been developed for single-nucleus assay for transposase-accessible chromatin using sequencing (snATAC-seq). One known caveat of droplet microfluidics, however, is that Poisson loading of cells or nuclei into emulsion oil droplets results in a significant proportion of droplets being loaded with >1 cell/nucleus. These technical artifacts known as ‘doublets’ can confound data analysis by appearing as ‘hybrid’ or ‘intermediate’ cell states that do not exist in reality.

I solved this issue by developing DoubletFinder (**McGinnis**, et al., *Cell Systems*, 2019), which was the first computational method for systematic doublet identification in scRNA-seq data. DoubletFinder finds doublets by identifying cells that co-localize in gene expression space with artificially-generated doublets. DoubletFinder has been broadly used by the single-cell genomics community and inspired the development of complementary methods. However, one caveat with community-detection based doublet detection algorithms is that they perform sub-optimally on snATAC-seq data. In contrast, methods such as AMULET (Thibodeau*, Eroglu*, **McGinnis**, et al., *Genome Biology*, 2021), which leverage the trinary nature (0, 1, or 2) of snATAC-seq data to identify doublets as nuclei with elevated levels of bi-allelic read counts, perform better in this context. My specific role in the DoubletFinder project involved conceiving and implementing the method, performing all bioinformatics analyses, and writing the manuscript. For the AMULET project (collaboration with Dr. Duygu Ucar’s group at JAX), I generated benchmarking datasets for measuring AMULET performance and aided in bioinformatic analysis.

Beyond my research focusing on doublet detection, I also contributed to the development of single-cell analysis methods such as DECIPHER-seq (Murrow, Weber, Caruso, **McGinnis**, et al., *Cell Systems*, 2022), which identifies high-confidence intercellular signaling interactions in complex biological systems using integrative non-negative factorization. Moreover, I helped develop D-SPIN (Jiang*, Chen*, Tsou, **McGinnis**, et al., *BioRxiv*, 2023), which is a statistical framework for modeling the cellular responses to chemical perturbation using scRNA-seq data. My specific roles in the DECIPHER-seq and D-SPIN projects (collaboration with Dr. Matt Thomson’s group at Caltech) involved generating scRNA-seq datasets, aiding in bioinformatic analyses, and contributing to manuscript writing.

1. **McGinnis CS**, Murrow LM, Gartner ZJ. “DoubletFinder: doublet detection in single-cell RNA sequencing data using artificial nearest neighbors.” *Cell Systems*. 2019; 8(4):329-37.e4. PMCID: PMC6853612.
2. Thibodeau A*, Eroglu A*, **McGinnis CS**, et al. “AMULET: a novel read count-based method for effective multiplet detection from single nucleus ATAC-seq data.” *Genome Biology*. 2021; 22(1):252. PMCID: PMC8408950.
3. Murrow LM, Weber RJ, Caruso JA, **McGinnis CS**, et al. “Mapping hormone-regulated cell-cell interaction networks in the human breast at single-cell resolution.” *Cell Systems*. 2022; 13(8):644-664.e8. PMCID: PMC9590200.
4. Jiang J*, Chen S*, Tsou T, **McGinnis CS**, et al. “D-SPIN constructs gene regulatory network models from multiplexed scRNA-seq data revealing organizing principles of cellular perturbation response.” *bioRxiv* [Preprint]. May 20, 2023. Available from: https://doi.org/10.1101/2023.04.19.537364.

C3. Single-cell genomics sample multiplexing

Since scRNA-seq was developed in early 2010s, it has predominantly been used to perform descriptive analyses of biological systems. For example, numerous ‘Cell Atlas’ research programs are currently underway that involve sequencing millions of cells spanning a variety of tissues and organ systems in diverse organisms. These efforts are undeniably important, as they will significantly update the cellular ‘parts-lists’ first canonized using anatomical and histological observations. However, to employ scRNA-seq for mechanism/hypothesis testing, existing scRNA-seq cell-throughput capabilities must be leveraged in a way that enables large numbers

of distinct samples (e.g., donors, time-points, replicates, etc.) to be processed in a pooled format. Until recently, this has been impossible due to technical constraints and high reagents costs.

I solved this issue by developing MULTI-seq (**McGinnis***, Patterson*, et al., *Nature Methods*, 2019), a method for scRNA-seq **s**ample **m**ultiplexing **u**sing **l**ipid-**t**agged **i**ndices. MULTI-seq is one of a family of scRNA-seq sample multiplexing technologies that involve labeling cell or nuclear membranes with sample-specific DNA barcodes prior to single-cell isolation. By barcoding cells before isolation, distinct samples can be processed in a pooled rather than parallel format, resulting in dramatically reduced reagent costs, increased cell-throughput, and improvements in data quality. MULTI-seq is unique amongst other sample multiplexing methods due to its universality – i.e., MULTI-seq will work on all biological entities with a lipid bilayer, enabling its application to cells and nuclei from any species. We leveraged this feature to analyze human metastases and mouse immune cells in the metastatic niche of a patient-derived xenograft mouse model of breast cancer – experiments which first inspired my interests in cancer immunology and metastasis biology. My role in the MULTI-seq project involved implementing the method, performing all experiments and bioinformatics analyses, and writing the manuscript.

To make MULTI-seq available to the global scientific community, I established a pipeline for distributing MULTI-seq reagents, protocols, and bioinformatics tools to interested users. During my time at UCSF, I sent MULTI-seq materials to >350 labs in 21 different countries and consulted on study design, sample preparation protocols, and bioinformatics analysis with a significant portion of these users. Moreover, I directly collaborated with researchers at UCSF and Caltech on a variety of projects leveraging MULTI-seq. For example, with Dr. Max Krummel's lab at UCSF, I helped develop a method for spatial transcriptomics called ZipSeq that leverages MULTI-seq technology (Hu, Eichorst, **McGinnis**, et al., *Nature Methods*, 2020). Moreover, with Dr. Thomson's lab at Caltech, I leveraged MULTI-seq to perform one of the first scRNA-seq-coupled high-throughput chemical compound screens on primary human immune cells. (Jiang*, Chen*, Tsou, **McGinnis**, et al., *BioRxiv*, 2023). Finally, with Dr. Ophir Klein's group at UCSF and Cedars-Sinai, I contributed both experimentally and computationally to multiple studies of intestinal epithelial cells. These studies led to two key discoveries; first, that the small intestine is segmented into 5 functionally-distinct domains, in contrast to the prevailing ilium/duodenum/jejunum model (Zwick, Kasparek*, Palikuqi*, Viragova*, Weichselbaum*, **McGinnis***, et al., *Nature Cell Biology*, 2024); and, second, that gut vilification is driven by a mesenchymal dewetting mechanism (Huycke*, Häkkinen*, Miyazaki*, Srivastava, Barruet, **McGinnis**, et al., *Cell*, 2024).

1. **McGinnis CS**,* Patterson DM*, et al. "MULTI-seq: sample multiplexing for single-cell RNA sequencing using lipid-tagged indices." *Nature Methods*. 2019; 16(7):619-26. PMCID: PMC6837808.
2. Hu KH, Eichorst JP, **McGinnis CS**, et al. "ZipSeq: Barcoding for Real-time Mapping of Single Cell Transcriptomes." *Nature Methods*. 2020; 17(8):833-43. PMCID: PMC7891292.
3. Zwick RK, Kasparek P*, Palikuqi B*, Viragova S*, Weichselbaum L*, **McGinnis CS***, et al. "Epithelial zonation along the mouse and human small intestine defines five discrete metabolic domains." *Nature Cell Biology*. 2024; 26(2):250-262. PMID: 38321203.
4. Huycke TR*, Häkkinen TJ*, Miyazaki H*, Srivastava V, Barruet E, **McGinnis CS**, et al. "Patterning and folding of intestinal villi by active mesenchymal dewetting." *Cell*. 2024; S0092-8674(24)00465-3. PMCID: PMC11166531.

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/christopher.mcginnis.1/bibliography/public/